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JEFF LLOYD
2421 N.W. 41ST STREET
SUITE A-1
GAINESVILLE, FL 32606-6669

EXAMINER	
LUCAS, ZACHARIAH	
ART UNIT	PAPER NUMBER
1648	13

DATE MAILED: 10/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/073,065	MOHAPATRA ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 21-23* is/are pending in the application.

4a) Of the above claim(s) *1,2,5 and 6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,4 and 21-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6,7,10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group II in Paper No. 12 is acknowledged. The traversal is on the ground(s) that there is no undue burden in the examination of the separate inventions (esp. Groups I-III). In support of that assertion, the Applicant points to the common classification of the claimed subject matter. The Applicant also traverses the restriction between the protein antigen vaccines and the gene expression vaccines on the grounds that the term antigen as it was intended to be used by the Applicant was intended to include both proteins and other molecules.

These arguments are not found persuasive. First, with respect to the restriction between Groups I to III, the Traversal is not found persuasive because the common classification of the inventions does not demonstrate that separate searches are required for the separate inventions. As was pointed out in the restriction requirement, such separate searches are required for the separate inventions, demonstrating burden. The restriction among these Groups is therefore maintained.

With respect to the Applicant's traversal of the restriction between the respiratory syncytial virus (RSV) protein antigen compositions, and the gene expression vaccines, the traversals are also not found persuasive. For example on each of pages 3, 6, and 14, the specification refers to antigens as encoded by the polynucleotides. Thus, the specification, in addition to the separate claiming of antigens and gene expression vaccines in the claims as filed demonstrates a distinction between the protein antigens and the DNA expression vaccine.

Further, the definition of antigen in the art, as provided (e.g.) in Stedman's Online Medical Dictionary, indicates that an antigen is expected to react with the antibodies or immune cells stimulated by the antigen. The gene expression plasmids of the Applicants gene expression vaccine would not react with the anti-RSV antibodies or cells. Thus, the Applicants explanation for their intention regarding the use of the term "antigen" is inconsistent with that in the art. In such cases, a clear definition of what is meant by the term is required in the application. See MPEP § 2173.05(a). As the Applicant has provided no such clear definition in the specification, the terms are provided the definitions used in the art. However, in view of the cancellation of the claims reading on the gene expression vaccines, the traversal is found moot. While the Applicant presents claims 21-23 as reading on such vaccines, these claims are clearly drawn to protein antigens encoded by gene expression vaccines, and not to the polynucleotide compositions themselves.

The requirement, as described above, is still deemed proper and is therefore made FINAL.

2. Claims 1, 2, 5, and 6 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 12.

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on May 20, 2002, November 18, 2002, and February 20, 2003, are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

4. It is noted that all of the references cited in the IDS of May 20, 2002 were also cited in the IDS of November 18, 2002. The references were therefore crossed off on the later IDS, having already been considered by the Examiner in the earlier IDS.

5. It is further noted that the reference-listing page of the ID filed in May 2002 indicates that the page is 1 of 2 pages. However, no second page was found in the file, and all of the references submitted with the IDS were listed on page 1. Page 1 is therefore being treated as the complete reference listing of that IDS.

Specification

6. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See, 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: The claims under examination read on immunogenic compositions comprising RSV (protein) antigens. However, while the Application as filed provides written description support for the claimed invention in the originally filed claims, there does not appear to be any antecedent basis support in the specification for such compositions. It is noted that the specification does refer to compositions on pages 3 and 6 for compositions comprising such antigens. However, given the context in which the compositions are presented, these instances appear to be more directed to compositions comprising DNAs encoding the components of the claimed composition.

Claim Objections

7. Claim 23 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claim reads on an immunogenic composition of RSV antigens as defined in claim 21, wherein "said plasmid DNA cocktail..." While claim 21 refers to one or more plasmid DNAs, it does not refer to a plasmid cocktail.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claim reads on an anti-RSV vaccine comprising an M2 RSV antigen and at least one other RSV antigen. The claim is not enabled as the Applicant has not demonstrated that the claimed composition would be an effective vaccine against RSV infection.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

In the present case, as indicated above, the Applicant's claims read on any mucosal vaccine comprising an M2 antigen and at least one other RSV protein antigen. No working examples, or other evidence, is provided demonstrating that the claimed compositions would be effective vaccines. The Applicant has in effect asserted that the claimed composition would be an effective vaccine without providing any evidence of such, or any guidance that would lead those in the art to effective RSV vaccines.

In contrast to the claims in the application, the art indicates that there is presently no safe and effective anti-RSV vaccine. See e.g., Brandenburg et al. (Vaccine 19: 2769-82). See also, Domachowske et al. (Clin Microbiol Rev 12: 298-309- of record in the IDS of May 2002, teaching on page 305 that, although there a several potential vaccines against RSV in development, no vaccines are currently available; and identifying some of the challenges involved in developing anti-RSV vaccines). Thus, the art teaches that anti-RSV vaccine development is a complex, and unpredictable art, with no safe and effective vaccines available

which one skilled in the art could use a comparison to determine that the claimed vaccine is likely to be effective. This is true in spite of the fact that all of the antigens identified by the Applicant were known in the art. See, Domachowske, page 300-301, and Connors et al., J Virol Volume 65, pages 1634-37 (of record in the May 02 IDS). In view of the limited teachings in the application, and the teachings of the art indicating that the claimed composition is not likely to be an effective vaccine, the Applicant is not enabled for a mucosal vaccine comprising the immunogenic composition of claim 3.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

11. Claims 3, 4, and 21-23 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Collins et al. (U.S. Patent 5,264,957, Collins I). The claims describe immunogenic compositions comprising an RSV M2 antigen and at least one other RSV antigen. Claim 4 is interpreted in this rejection as further limiting the composition of claim 3 to compositions for mucosal administration. Claims 21-23 specify a source of the antigens in the claimed composition. Collins I teaches the making of a RSV particle using a number of plasmid vectors.

Collins I teaches the production of RSV viral particles through transfection of plasmids encoding for the M2 antigen and at least one other RSV antigen as defined in claim 3. Col. 8,

lines 18-53, and cols. 15-19. The reference also teaches that the RSV particles so created may be used in immunogenic compositions. Columns 4-5, and 11-12. Further, the reference teaches that the RSV composition may be formulated for oral (thus, mucosal) administration. Column 12, lines 1-5. In view of the teachings described above, the reference either anticipates, or renders obvious the claimed immunogenic compositions.

It is noted that the reference does not specifically teach the use of plasmid DNA coacervated with chitosan to form nanospheres. However, the reference does state that the plasmids encoding the viral proteins (and antigenome) may be transfected through a number of methods. Column 8, lines 18-39. While not specifically indicating that the plasmids may be coacervated with chitosan, the discussion of transfection in the reference indicates that any known method of transfection may be used. The method identified in claim 23 was known. See, Leong et al. (J Controll Release 53: 183-93). Leong teaches that chitosan nanoparticles were effective delivery agents of DNA plasmids into cells. Pages 188-89. As the Applicant has not demonstrated that the use of such nanospheres would result in a structurally different immunogenic composition, it seems as though the methods taught by Collins I would result in a structurally identical immunogenic composition to that resulting from the use of the method described in claim 23.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 3, and 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Collins et al. (PNAS 92: 11563-67, Collins II). These claims read on anti-RSV immunogenic compositions comprising an M2 antigen with at least one other RSV antigen. Collins II teaches the rescue of an infectious RSV particle from a cell transfected with plasmid cDNA encoding RSV N, P, L, and M2 proteins, and a cDNA encoding the antigenome of the virus. Page 11564. The reference further teaches that this method of rescuing infectious RSV can be used to produce attenuated forms of the RSV virus (RSV immunogenic compositions). Pages 11566-67. As the reference teaches a method of RSV rescue comprising the use of M2, P, L, and N proteins encoded by plasmid DNAs, and the use of such a method to prepare immunogenic compositions against RSV, the reference renders the claimed compositions obvious. While the reference does not teach the use of plasmid DNA coacervated with chitosan to form nanospheres, the Applicant has not demonstrated that the use of such nanospheres would result in a structurally different immunogenic composition.

For example, Leong et al. (J Controll Release 53: 183-93) teaches that chitosan nanoparticles were effective delivery agents of DNA plasmids into cells. See e.g., Leong, pages 188-89. Thus, it is clear that one of ordinary skill in the art would have known how to, and could have used chitosan/DNA nanospheres for the plasmid transfection of cells in the method taught by Collins. In view of the above, the Collins II reference renders the claimed invention obvious.

14. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Collins as applied to claim 3 above, and further in view of Wright et al. (J Infect Dis 182(5): 1331-42). Claim 4

reads on the immunogenic composition of claim 3, wherein the composition is a mucosal vaccine. For the purposes of this rejection, the claim is treated as reading on a mucosal immunogenic composition. The teachings of Collins have been described above. The reference does not teach the mucosal administration of the attenuated virus. Such a teaching is, however, provided in Wright, which indicates that attenuated RSV may be administrated intranasally (therefore mucosally) to induce an immune response. See e.g., Abstract. The combined teachings of the references therefore render the identified claim obvious.

15. Claims 3, and 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Domachowske (supra) in view of the teachings of Hsu et al. (J Gen Virol 80: 1401-05) and Simmons et al. (J Immunol 166(2): 1106-13). The claims have been described above. Domachowske teaches that the RSV F and G proteins result in the formation of anti-RSV antibodies. Page 301. The reference also teaches the RSV M2, N, F, and SH, and NS2 proteins are targets for CTL responses in humans. Id. However, the reference does not teach the combination of the M2 protein with other RSV antigens to achieve an immune response.

Hsu teaches that a superior immunogenic response is induced by the administration of antigens that induce both humoral and CTL responses than would result from the administration of either antigen alone. See e.g., page 1404, first Discussion paragraph. Thus, the reference teaches those in the art that, for inducing an anti-RSV response, it is preferable to administer to a subject a combination of both humoral and CTL inducing antigens. Simmons teaches that a region of the M2 protein is an effective CTL inducing antigen.

In view of these teachings, it would have been obvious to those in the art to combine an M2 antigen with either of the G or F proteins of RSV to induce an immune response. The motivation to combine these antigens is, as suggested by Hsu, to achieve a superior anti-RSV immune response. There would have been a reasonable expectation of success in achieving a more effective immunogenic composition through such a combination as both the G and F proteins are known to induce humoral immune responses and M2 is known to induce a CTL response (Domachowske and Simmons). Because of these known protein characteristics, and because it was also known that a combination of humoral and CTL antigens resulted in a superior anti-RSV responses (Hsu), those in the art would have had a reasonable expectation that a combination of M2 and either of the F or g proteins would result in a superior immunogenic composition than any of the antigens alone. The combined references therefore render the claimed compositions obvious.

It is noted that the identified references do not teach how the claimed RSV antigens were formed. However, as indicated in the rejection over Collins above, the Applicant has not demonstrated the method of forming the antigens described in the claims would result in RSV antigens structurally different from those in the prior art.

16. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Domachowske in view of Hsu and Simmons as applied to claim3 above, and further in view of the teachings of Wyatt et al. (Vaccine 18: 392-97- of record in the May 2002 IDS). The claim has been described above. As above, the claim is treated as reading on a mucosal immunogenic composition. The teachings of Domachowske and Hsu, and the teachings, in part, of Simmons, have been

described above. Simmons additionally teaches that an M2 peptide antigen may be effectively administered mucosally. Wyatt teaches that mucosal administration of either of the F and G proteins induces a greater antibody response than is detected when the antigens are administered by other means. Thus, as the art teaches that both the M2 and the F or G antigens may be effectively administered mucosally, and as the art suggests the combination of the antigens as described above, it would have been obvious to those in the art to formulate the combined immunogenic composition for mucosal administration.

Conclusion

17. No claims are allowed.

18. The following prior art references are made of record and are considered pertinent to applicant's disclosure. However, while relevant they are also not used as a basis for rejection for the stated reasons.

Connors et al., J Virol 65(3): 1634-37 (supra). The teachings of this reference suggest that the RSV M2 antigen may be useful in inducing a CTL response against the virus. Page 163, left column. However, the reference does not suggest the combination of this antigen with other RSV antigens. The reference is considered as redundant to Domachowske.

Chanock et al., Pediatrics 1992, pp. 137-41 (of record in the Nov 2002 IDS). This reference teaches that four of the 10 RSV proteins, the F, G< N, and M2 proteins, are immunogenic.

Wertz et al., WO 87/04185. For the purposes of this action, this reference is considered redundant to the teachings of Domachowske and Collins I and II. See e.g., page 6, and claims 1, 8, 12 and 14.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 703-308-4240. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Z. Lucas
Patent Examiner

JAMES HOUSEL 10/20/03
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600